Marking the 50th Anniversary of *Immunology*

Special regulatory T-cell review: suppressors regulated but unsuppressed[1]

Judith A. Kapp

Department of Ophthalmology, University of Alabama at Birmingham, Birmingham, AL, USA

Summary

The rise-and-fall and reincarnation of suppressor T cells is reviewed from the perspective of a participant in the field.

Keywords: suppressor T cells; regulatory T cells

Although various methods for inducing tolerance were identified after the original report of oral tolerance by Wells in 1911,[1] it was not appreciated that tolerance could be actively maintained until Gershon's seminal reports published by *Immunology* in 1970 and in 1971. Gershon showed that thymus-derived lymphocytes were not only required for tolerance induction[2] but that they could adoptively transfer tolerance to naïve recipients.[3] This form of tolerance, dubbed 'infectious tolerance', was antigen-specific and the T cells that inhibited responses were operationally defined as suppressor T cells, in distinction from helper T cells.[4] Suppressor T (Ts) cells were later identified as Ly2,3+ (CD8+) T lymphocytes.[5,6] These observations prompted us to test whether Ts cells played a role in major histocompatibility complex (MHC)-linked unresponsiveness. Our experiments demonstrated that unresponsiveness to certain synthetic polypeptide antigens[7] and proteins closely related to self antigens such as insulin[8] was maintained by CD8+ Ts cells. The ability of antigen-specific CD8+ T cells to adoptively transfer non-responsiveness was convincingly demonstrated by numerous investigators using a variety of experimental systems (reviewed in refs 9,10).

After an explosion of studies in the 1970s, interest in Ts cells fell precipitously in the mid- to late 1980s from a convergence of several findings, none of which was individually fatal but collectively they led to the demise of this field. First, the newly developed methodology to generate long-term lines and clones of T cells yielded very few stable, CD8+ T cells with antigen-specific suppressive activity. Second, no coding region corresponding to the Ts-cell-associated serological determinant, referred to as I-J, was evident when a physical map and complete sequencing of the MHC was accomplished.[11] Nor did we find RNA transcripts from Ts-cell hybridomas that could hybridize to cosmid clones spanning the I-A and I-E subregions of the MHC.[12] Third, the biochemical nature of the soluble suppressor factors, which were extracted from Ts cells or elaborated by Ts-cell hybridomas, was not elucidated despite strenuous efforts by several laboratories including my own. Fourth, once it was recognized that CD8+ cytotoxic T lymphocytes recognized endogenous peptides in association with MHC class I proteins, it was thought that CD8+ Ts cells should not be able to recognize exogenous protein antigens. Fifth, and perhaps most critical, was that the focus of immunological research shifted to the molecular identification of critical elements of immune responses, which met with unprecedented success. In the dawning of the age of molecular immunology, the complex circuits of interacting cells and ill-defined factors that were associated with the Ts field came to be regarded as untenable. Consequently, fewer and

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Abbreviations: APC, antigen-presenting cells; IL-2, interleukin-2; MHC, major histocompatibility complex; TCR, T-cell receptor; Tg, transgenic; TGF-β, transforming growth factor-β; Th, T helper; Treg, T regulatory cells; Ts, T suppressor cells.

fewer studies of CD8$^+$ Ts cells were funded and interest in these cells dissipated, although it never totally disappeared.

The concept that T cells are involved in immunological tolerance through active suppression was resurrected by the observations that a distinct subset of naturally occurring CD4$^+$ CD25$^+$ T cells from naïve mice have the capacity to prevent autoimmune disease mediated by endogenous, self-reactive T cells.[13] The expression of CD25 by regulatory T (Treg) cells in naïve mice proved to be decisive because it allowed them to be physically isolated from other CD4$^+$ T cells and shown to be the mediators of immunosuppression. To avoid the 'politically incorrect' term of 'suppressor T cells',[14] these cells came to be known as regulatory T (Treg) cells, which was an unfortunate choice because the term 'regulatory' encompasses both positive and negative effects.

CD25 expression identified Treg cells among naïve T cells that had not been experimentally exposed to antigen. However, CD25 is not a unique Treg marker because it is also expressed by effector T cells upon antigen activation. As yet, no cell surface antigen has been identified that serves as a lineage marker that is exclusively expressed by Treg cells (or CD8$^+$ Ts cells). The prominence of Treg cells was substantially boosted by the identification of a transcription factor from the forkhead/winged helix family, FoxP3[15,16] as a master switch that drives the differentiation of naïve T cells into the Treg lineage and maintains their suppressive function.[16–20] Antibodies to murine FoxP3 became available to identify cells expressing this intracellular molecule,[21–23] but it was the construction of FoxP3 reporter (FoxP3^{gfp}) mice, which faithfully express green fluorescent protein when FoxP3 is synthesized, that allowed FoxP3$^+$ cells to be sorted by flow cytometry and to be shown to be responsible for the regulatory activity of CD4$^+$ T cells.[24–26]

The Treg cells express conventional αβ T-cell receptors (TCR) and block autoimmunity, which strongly suggests that they recognize self antigens, yet it has been difficult to define the repertoire of epitopes recognized by these cells. The observations that Treg cells can be induced from peripheral CD4$^+$ CD25$^-$ T cells by stimulation with exogenous antigens presented via a tolerogenic route[27,28] or by activation in the presence of transforming growth factor-β (TGF-β) [29,30] and that induced Treg cells also express FoxP3[30,31] has allowed the application of TCR transgenic (Tg) T cells to the study of specificity and mechanisms of action of Treg cells (reviewed in ref. 32). Collectively, these results suggest that most, if not all, naïve CD4$^+$ T cells may be capable of becoming Treg cells under the appropriate conditions. If the latter hypothesis is correct, then the apparent differences between natural and induced Treg cells may simply reflect the solidification of the expression of FoxP3 arising from chronic *in vivo* stimulation by autoantigens versus acute activation

by exogenous antigens. This process would be analogous to the characteristic way in which CD4$^+$ T cells become irreversibly committed to T helper type 1 (Th1) and Th2 phenotypes by prolonged repetitive *in vitro* stimulation in the presence of the appropriate cytokines.

Breeding TCR Tg mice with the FoxP3^{gfp} reporter mice allowed us to demonstrate that CD4$^+$ FoxP3$^+$ TCR Tg T cells, induced by activation with antigen in the presence of TGF-β and interleukin-2 (IL-2), are similar to natural Treg cells in their ability to inhibit proliferation and effector responses by naïve T cells.[33] However, the ability of FoxP3$^+$ T cells to inhibit the responses of T cells specific for other antigens depended on the expression of the Treg epitope and the effector epitope by the same antigen-presenting cells (APCs).[33] This phenomenon was originally termed 'linked-suppression' by Holan and Mitchison[34] and this pattern of specificity has been validated in multiple experimental systems.[35–39] Our finding that Treg cells are specific both in activation and in effector function *in vitro* correlates with data indicating that Treg cells have exquisite functional specificity *in vivo*.[39–42] Identifying an analogous specificity pattern among polyclonal natural Treg cells is experimentally problematic, because syngeneic APCs expressing self antigens can interact with both Treg cells and effector T cells specific for exogenous epitopes, which can be misinterpreted as non-specific suppression. Whether Treg cells and naïve responder T cells directly interact within the confines of an APC-initiated cluster or whether these two T cell types interact sequentially with the same APC, as has been shown for helper T cells,[43] is not yet known. Nevertheless, the observation that Treg cells and responder T cells must recognize the same APC provides a mechanistic explanation for the often reported, but poorly understood, requirement that Treg cells must be in direct contact with effector T cells to inhibit their responses.

Interest in the role of CD8$^+$ Ts cells was renewed, in part, by the observations that they could be activated by antigen in the presence of TGF-β.[44,45] Antigen-specific, CD8$^+$ Ts cells have also been described in the blood of rejection-free human cardiac transplant recipients[46,47] and FoxP3 is up-regulated in human[48] and rat[49] CD8$^+$ CD28$^-$ Ts cells from stable transplant recipients. The TGF-β-activated TCR Tg CD8$^+$ T cells,[50] and the donor-specific CD8$^+$ Ts cells from transplant patients[46,51] also exhibit linked-suppression, suggesting that suppression is most efficiently mediated by direct cell contact rather than by the elaboration of cytokines. Although TGF-β-activated TCR Tg CD8$^+$ T cells fail to proliferate upon restimulation, they express FoxP3 and also down-modulate the expression of CD86 by dendritic cells,[50] which is consistent with the central role of APCs in mediating suppression. Preliminary data, using CD8$^+$ T cells from TCR Tg mice expressing the FoxP3^{gfp} allele, suggest that the FoxP3$^+$ cells are antigen-specific Ts cells, but it is not yet

clear whether they are the only cells with suppressive activity in the cultures stimulated with antigen, TGF-β, and IL-2 (Kapp *et al.*, unpublished observations).

At this juncture, it seems reasonable to reflect on what we have learned about CD8^{+} Ts cells in the last 20 years that sheds light on the issues that caused the convulsive rejection of the whole body of suppressor T-cell literature and ridicule of the investigators who studied them. Several of the findings that contributed to the demise of the Ts-cell field have actually been resolved. First, Treg and Ts cells have been shown to have little or no capacity to proliferate *in vitro* when stimulated with antigen or polyclonal activators, especially in competition with effector T cells. Therefore, the conditions typically used to establish T-cell lines, which were biased toward rapid growth, did not generate either Treg or Ts cell lines. Only recently have investigators devised alternative methods of growing Treg[52] and CD8^{+} Ts cells[53] *in vitro*. Second, it is now well-recognized that CD8^{+} T cells can be stimulated by exogenous proteins that are taken up and processed into the MHC class I pathway by professional APCs such as dendritic cells and macrophages (reviewed in refs 54–56) or antigen-specific B cells that bear surface immunoglobulin capable of binding the native protein.[57] Third, the interacting suppressor inducers, suppressor effectors and contra-suppressors, once judged to be too complex to be tenable, are not dissimilar to the complexity of functional T-cell phenotypes that have now been distinguished by the patterns of cytokines that they produce. Already, Th0, Th1, Th2, Th3, Tr1, Th17, Tc1, Tc2, lytic CD8^{+} and non-lytic CD8^{+} Ts-cell subsets have been identified, which interact in complex and only partially understood pathways to maintain homeostasis. Thus, the concepts that immune regulatory mechanisms are complex and that both CD4 and CD8 T cells can actively mediate suppression, or negative regulation, are now accepted as fundamental immunological principles.

Other findings that contributed to the demise of Ts cells have not been explained, but there are plausible explanations for these phenomena. First, the puzzle of the I-J determinants recognized by alloantibodies produced across MHC differences has not been solved. It is, however, conceivable that these antibodies recognize idiotypic determinants of the peptide MHC binding surface of the TCR or even peptide–MHC complexes that are captured by T cells from APCs during formation of the immunological synapse (reviewed in ref. 58). Second, the molecular nature of the soluble antigen-specific suppressor factors has not been elucidated. However, it is now well-established that naturally occurring, soluble forms of a variety of cell surface receptors, such as tumour necrosis factor[59] and IL-6 receptors,[60] act as potent inhibitors of the pathways activated by the ligands that bind to them. This raises the possibility that the biological activity of suppressor factors may have been mediated by soluble TCR, which could interfere with full signalling between T cells and APCs by inhibiting the kinetics of aggregation in the immunological synapse. Only time will tell whether these explanations will be tested or whether answers may arise from unrelated investigations.

Regardless of where future studies of Ts cells may take us, it is important to me to try to understand why we failed in these endeavours 20 years ago. These studies were not performed by just a few individuals operating in obscurity. Dozens of investigators on four continents worked in this area and hundreds of papers were published on this topic. At least 10 major independent laboratories worked (and competed with each other) on these problems using an extensive variety of assay systems over a period of more than 10 years. Although it is difficult to understand why solutions were not obtained, it seems unlikely that we suffered from a collective delusion or that the data were selectively biased or faked on such a grand scale, as some have implied. To me, it seems more likely that the assays and tools that were available were not robust enough to solve these problems. The lack of success begat a decrease in funds, lowering the chances of subsequent success, until funding totally collapsed and the study of these bioactive factors was abandoned. So, we are left with the less than satisfying conclusion that the absence of proof concerning I-J and suppressor factors is not proof of their absence.

Acknowledgements

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